J. Pharm. Pharmacol. 1988, 40: 205–207
Communicated November 5, 1987

Gastric emptying of large single unit dosage forms

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Abstract—The gastrointestinal transit of two single unit dosage forms has been followed in healthy subjects under different feeding conditions. Transit was affected by the size of the meal administered. When two tablets were given concurrently they often emptied from the stomach at or about the same time, but in a number of cases the two units were seen to empty at widely different times.

In recent years there have been many reports in the pharmaceutical literature describing studies on the gastrointestinal transit of a variety of dosage forms in human subjects using the technique of gamma scintigraphy (Fell & Digenis 1984; Davis et al 1986b). Clear differences in the gastric emptying behaviour have been established for multiple units and single units that can be related to particle size and the quantity of food in the stomach (Davis et al 1984). Small particles (those less than about 5 mm) can empty from the fed stomach while larger objects are retained until the stomach is empty of food, and then cleared by the physiological mechanism known as the migrating myoelectric complex (MMC) (Kelly 1981). Here waves of contractile activity 'sweep' undigested material from the stomach and down the small intestine with a periodicity of about 2 h.

On the basis of these results, it is to be expected that one, two (or more) large units should be retained in the fed stomach for a period of time proportional to the size (calorific value) of the meal administered and then should empty together under the action of the MMC. In the present work, eight subjects were given two tablets of 12 mm diameter and the gastric emptying behaviour measured after a light (1500 kJ) and a heavy breakfast (3000 kJ).

Methods

Tablets of 12 mm diameter were produced by compressing hydroxypropyl methylcellulose on a Manesty F3 machine. The powder mix contained a small quantity of ground ion-exchange resin (Amberlite IR120(H)) labelled with the gamma emitting material indium-111 as described previously (Davis et al 1984). The tablets of approximate density 1·3 g cm^{-1} were coated with a layer of ethylcellulose to prevent their disintegration.

The tablets were administered to 8 healthy, non-smoking male subjects (four per group) (age range 18–22, weight range 68–85 kg, height range 1·70–1·92 m) according to a randomized two-way crossover design following a standard breakfast of either 1500 kJ (light breakfast) or 3000 kJ (heavy breakfast), together with 100 mL of water. The subjects were maintained on a standard diet during each part of the study. Four hours after dosing the subjects were allowed to eat a standard lunch to reflect a real-life situation where patients would take controlled release oral medication with or soon after breakfast and then followed normal dietary practice.

The position and outline of the stomach and the subsequent emptying of the single unit(s) was established by the concomitant administration of a pellet system labelled with technetium-99m (Transitest, Nielsen et al 1986). The indium-111 and technetium-99m have different photopeak energies and the administration of the pellets did not interfere with the image of the tablets. The position(s) of the tablets in the gastrointestinal tract was followed by placing the subjects in front of a gamma camera (MaxiCamera—GEC, 40 cm field of view) and taking scintiphotos at intervals over a 12 h period. Gastric emptying was determined by reference to an external anatomical marker that took the form of a technetium-99m labelled adhesive patch attached to the subjects just below the ribs. Each tablet had about 0·25 MBq activity and the pellets had about 5 MBq activity at the time of administration. One week after receiving the first breakfast the crossover was performed. The study was approved by the Ethical Committee of the University of Nottingham and conducted according to the guidelines of the Declaration of Helsinki.

Results and discussion

Representative scintiphotos are shown in Fig 1 and 2. Those in Fig. 1 demonstrate different events in gastric emptying, namely (a) two tablets in the stomach, (b) two tablets that have emptied concurrently into the small intestine, (c) one tablet that has emptied from the stomach but with one tablet remaining in the stomach. Events related to the movement of tablets from small

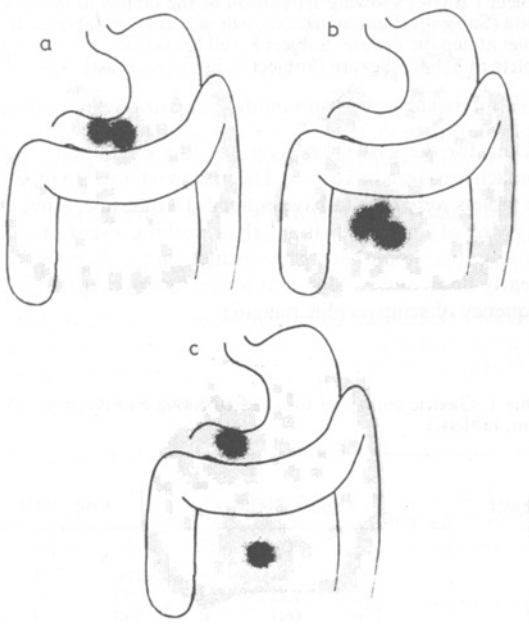

FIG. 1. Scintigraphic images demonstrating different events in gastric emptying. (a) Two tablets in stomach (Subject 2, light breakfast), 38 min. (b) Two tablets that have emptied concurrently to the small intestine (Subject 2, light breakfast), 606 min. (c) One tablet remaining in stomach, one tablet emptied into small intestine (Subject 8, full breakfast), 270 min. The outlines of the stomach and colon have been superimposed on scintiphotos by reference to the external market and the transit of concomitantly administered labelled pellets.

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to large intestine through the ileocaecal sphincter are given in Fig. 2, namely (d) two tablets at the ileocaecal junction (ICJ), (e) the same subject studied 1 h later where separation of the tablets in the ascending colon is evident, (f) the situation where one tablet is held at the ICJ while the other is at the hepatic flexure and (g) two tablets that have traversed the ICJ concurrently and are situated at the hepatic flexure.

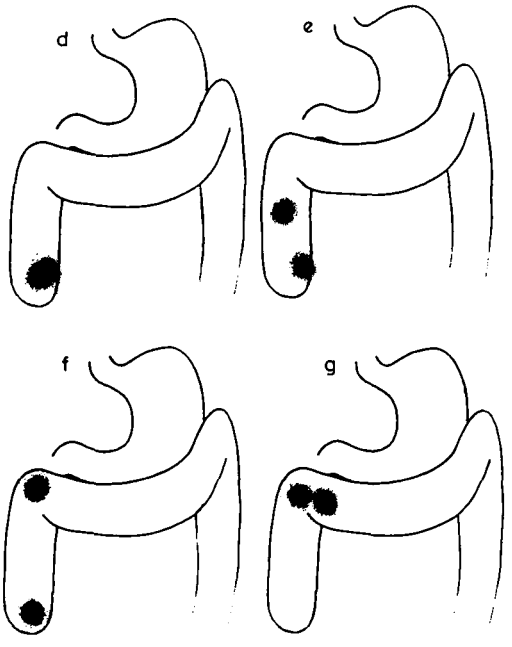

FIG. 2. Events in intestinal transit. (d) Two tablets at the ileocaecal junction (ICJ) (Subject 1, light breakfast), 480 min. (e) The same subject 1 h later showing separation of the tablets in the ascending colon (Subject 1, light breakfast), 540 min. (f) One tablet at ICJ, one tablet at hepatic flexure (Subject 8, full breakfast), 545 min. (g) Two tablets at hepatic flexure (Subject 3, light breakfast), 429 min.

Data for the gastric emptying of two single units from the stomach are given in Table 1. The figures refer to the times when the tablets were seen to have entered the intestine. Since gastric emptying of single units is an 'all or nothing' event, these times are only approximate and have an uncertainty of about ± 10 min at early times and ± 30 min at longer times, depending on the frequency of scintigraphic imaging.

Table 1. Gastric emptying times of two single units (min). (12 mm diam. tablets.)

Subject	Breakfast: Light (1500 kJ)			Full (3000 kJ)		
	T_1	T_2	ΔT	T_1	T_2	ΔT
1	150	200	50	260	310	50
2	600	600	0	690	690	0
3	120	160	40	550	550	0
4	200	200	0	270	490	220
5	215	215	0	250	250	0
6	115	220	105	570	570	0
7	610	670	60	520	520	0
8	310	310	0	180	670	490
Mean		306			459	
s.e.m. (n = 16)		49			44	

T_1,T_2 observed emptying times for individual tablets.
ΔT difference in emptying time.

For the study, the design should reflect well the typical real-life situation of dosing at breakfast time followed by normal dietary intake, but there was considerable variation between subjects in terms of the measured gastric emptying time. Such results suggest that variable absorption rates could occur from certain large single controlled release forms that contain drugs that are poorly released into the stomach (e.g. non-steroidal anti-inflammatory drugs), or those that rely on the release of a pH sensitive coating (to include enteric coated products). The mean data show the expected effect of food on the gastric emptying of single units. For the light breakfast the mean emptying time was 306 ± 49 s.e.m. (n = 16), while for the heavy breakfast the mean time was 459 ± 44 s.e.m. (n = 16). Large tablets will be retained in the stomach while it contains food, but will be cleared by the subsequent action of Phase 3 of the MMC (Szurszewski 1969). The larger the size of the meal, the longer the retention of the non-disintegrating tablets in the stomach.

In some individuals there is no real difference between the emptying behaviour of tablets after light and heavy breakfast (e.g. individuals 2, 5 and 7). This can be related to the fact that the subjects received the standard lunch at 4 h after dosing, i.e. before the stomach had completely emptied the breakfast, and therefore before the single units could be cleared by the action of the MMC.

The results show that the two tablets can empty concurrently or within 1 h of each other (ΔT in Table 1 = 0 for 9/16 and $\Delta T < 60$ min for 13/16). For some studies the tablets did not empty concurrently or at intervals less than 60 min. For example, in subject 6, light breakfast, ΔT is approximately 100 min and for subjects 4 and 8 after the heavy breakfast ΔT is 220 and 490, respectively. The short emptying time for one tablet in subject 8 after the heavy breakfast can be attributed to the phenomenon of 'fortuitous emptying'. Normally in the fed state the pyloric sphincter is contracted and only small objects (less than 5 mm) and liquids are able to empty into the duodenom. The contractions of the stomach in the digestive mode can cause a large object to be emptied fortuitously. Dozois et al (1971) have suggested that large objects occasionally become 'trapped' in the terminal antrum of fasted dogs. As the next peristaltic wave sweeps arborally, a high pressure differential exists between the stomach and duodenum, causing the object to empty through the open pylorus. Since the peristaltic activity of phase 2 is similar to that of the non-fasted state (Golub et al 1986) a similar situation can be envisaged in the present case.

The time of arrival of the single units at the ICJ is dependent on their gastric emptying behaviour. Data for the time of transit

Table 2. Small intestine transit times of two single units (min). (12 mm diam. tablets.)

Subject	Light breakfast (1500 kJ)	
1	325	275
2	80	120
3	115	155
4	145	145
Mean	170	
s.e.m. (n = 8)	30	
Subject	Full breakfast (3000 kJ)	
5	170	200
6	95	95
7	140	140
8	485	a
Mean	189	
s.e.m. (n = 7)	51	

a—Colon arrival time greater than 700 min due to long gastric emptying time of 670 min (Table 1).

of tablets in the small intestine were available for 4 subjects taking the light breakfast and 4 subjects taking the heavy breakfast (Table 2). Here there are no differences that can be attributed to the size of the breakfast and the mean transit time is about 3 h. This relative constancy in small intestinal transit time has been discussed in detail elsewhere by Davis et al (1986a).

Interestingly, the transit of single units through the ileocaecal sphincter, can, in some cases, result in one tablet moving to the ascending colon with the other remaining at the ICJ. Periods of stagnation at the ICJ (and also at the hepatic splenic flexure of the colon) are not uncommon and can be observed with single and multiple unit dosage forms (Khosla & Davis, unpublished) and with faecal masses in constipation. The differential transit of two single units through the ICJ indicates that the sphincter in this region may have some form of limiting function in controlling the transit of chyme from the small to large bowel. This role has been discussed in recent contributions from the Mayo Clinic (Quigley et al 1984).

Conclusions. Two large units administered together can either empty together (or within 1 h of each other) or at widely different times. The transit of two single units through the ileocaecal junction can also occur on a differential basis.

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J. Pharm. Pharmacol. 1988, 40: 207–209
Communicated July 28, 1987

Modulation of cyclic AMP and autoregulation of renal blood flow, analysed by the use of forskolin and 1-methyl-3-isobutylxanthine

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Abstract—We have examined the effects of forskolin and 1-methyl-3-isobutylxanthine (IBMX) in relation to cyclic (c)AMP metabolism and renal blood flow autoregulation in anaesthetized dogs. Control observations usually showed excellent autoregulation of renal blood flow over the renal perfusion pressure range of 120–200 mmHg, when the perfusion pressure was changed, stepwise, between 60 and 200 mmHg. Renal blood flow was increased by the infusion of forskolin (10 μg min^{-1}) and IBMX (100 μg min^{-1}) at the basal perfusion pressure of 100 mmHg, and maintained an increased level while the infusion was continued. Forskolin and IBMX did not inhibit autoregulation, though they shifted the perfusion pressure range evoking autoregulation. These data indicate that vasodilators which may produce the activity through modulating the cAMP level in vascular smooth muscle do not influence the establishment of autoregulation of renal blood flow.

Kidney is known to show autoregulation which maintains a stable renal blood flow level in spite of fluctuation of perfusion pressure. As the explanation of this mechanism, Thurau & Kramer (1959) have assumed the myogenic theory based on the experimental result that papaverine, by its "smooth muscle paralysing action", abolished renal blood flow autoregulation. We have expanded the theory demonstrating that intra-arterial infusion of Ca antagonistic vasodilators, such as verapamil, nifedipine and diltiazem, inhibited renal blood flow autoregulation (Ono et al 1974; Ogawa & Ono 1986a). We recently discovered, however, that certain vasodilators, such as nicorandil, sodium nitroprusside, sodium nitrite, prostaglandin E_2 and bradykinin had no effect on renal blood flow autoregulation despite causing an increase in renal blood flow (Ogawa & Ono 1985, 1986a).

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Thus, not all kinds of vasodilators inhibit renal blood flow autoregulation, and the inhibitory activity of some vasodilators has a different mechanism of action from their vasodilator activity.

In the present study, we have studied the effects of forskolin, which stimulates adenylate cyclase (Seamon & Daly 1981), and IBMX, which inhibits phosphodiesterase (Wells et al 1975), on renal blood flow autoregulation.

Materials and methods

Healthy mongrel dogs of either sex (n = 15), 9–15 kg, were sedated with morphine hydrochloride (2 mg kg^{-1} s.c.) and anaesthetized with α-chloralose (40 mg kg^{-1}) and urethane (400 mg kg^{-1}) intravenously. A femoral artery and vein were cannulated for the measurement of systemic blood pressure and administration of further anaesthetic and heparin. Pressure-controlled perfusion experiments were performed using the left kidney. Details of the procedure have been described previously (Ogawa & Ono 1985). The left renal artery was cannulated and perfused with blood from the carotid artery. An initial dose of 500 u kg^{-1} of sodium heparin was given as anticoagulant. Perfusion pressure was controlled by the use of a Starling's pneumatic resistance. Perfusion pressure and systemic blood pressure were each measured conventionally by means of a